## REMARKS

The Office Action mailed April 19, 2007 has been carefully considered and the following response prepared. Claims 3-10, 16 and 18-25 are pending in the application. Claim 20 has been canceled without prejudice.

At page 2 of the Office Action the Examiner rejected claims 3-10, 16, 18-21 and 23-25 under 35 USC 112, first paragraph as not enabled. The Examiner asserted that the specification, while enabling for a composition and a method for reducing the risk of postoperative ischemia reperfusion injury, does not reasonably provide enablement for a composition and a method which is effective in reducing the risk of any and all postoperative complications as instantly claimed. The Examiner stated that Applicant has not demonstrated that the composition and method are effective in reducing all postoperative complications. The Examiner cited Kerr et al., British Journal of Anesthesia, vol. 86(4), pages 586-589, 2000, which discloses an unusual case of intra-operative and post-operative hypercapnia, as evidence that the Applicant has not demonstrated the usefulness of the claimed compositions and methods for all postoperative complications. The Examiner further asserted that it would require undue experimentation without a reasonable expectation of success in order to determine the efficacy of the claimed composition and method in reducing the risk or any and all postoperative complications, as broadly claimed by Applicant.

Applicant traverses this rejection. The test of enablement is whether one skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The specification discloses the use of compositions comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, and/or one precursor of this NO donor, or the physiologically tolerated salts or combinations thereof to avert or reduce the risk of postoperative complications. The usefulness of the formulations for averting or reducing the risk of postoperative complications is exemplified in the specification for postoperative ischemia reperfusion injury. Applicant respectfully submits that the disclosures

in the patent application coupled with information known in the art thus allow persons skilled in the art to practice the invention as claimed without undue experimentation

The term "postoperative complications" encompasses different indications and is well-known in the art. Applicant submits herewith Clavien, P.-A. et al., Surgery vol. 111(5), pages 518-526, 1991 in Appendix A. Clavien et al. discusses postoperative surgical complications and sets out a general classification of complications by severity. Persons skilled in the art know and understand that even though various conditions may be present, these are still classified as postoperative complications.

Withdrawal of this section 112, first paragraph rejection is respectfully requested.

At page 4 of the Office Action, the Examiner rejected claim 20 under 35 USC 112, second paragraph as indefinite. Claim 20 has been canceled without prejudice and this rejection is now moot.

At page 5 of the Office Action, the Examiner rejected claims 3-10, 16, 18-19 and 21-25 under 35 USC 103 as unpatentable over Inanami et al. (Free Radic Res), Schneider et al (U.S. Patent 6,656,608), Sherrat et al (U.S. Patent 6,423,359) and Schneider et al. (U.S. Patent 5,902,829). The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the green tea extract taught by Inanami et al. and the glycine and glutamine taught by Schneider et al ('608 patent), Sherratt et al. and Schneider ('829 patent), to obtain a composition that would be useful for treating preoperative patients to reduce the risk of postoperative complications such as the oxidative injury caused by ischemia reperfusion. The Examiner further stated that the administration times taught by the cited references would render obvious the instantly claimed administration which takes place less than twenty-four hours before surgery. The Examiner asserted that adjustment of particular working conditions (e.g., administering the composition to a patient at an hour before or after surgery) is merely a judicious selection and routine optimization which is well within the abilities of the skilled artisan.

Applicants traverse this rejection.

Inanami et al. discloses oral administration of (-)catechin from green tea to gerbils for two weeks prior to surgery wherein the surgery induced transient focal brain ischemia. Administration of (-) catechin continued one week after surgery. The authors found that oral

administration of (-) catechin protected the animals against ischemia-reperfusion-induced neuronal death.

Schneider et al. (U.S. Patent 5,656,608) disclose the use of one or more of the amino acids glycine, alanine and serine in combination with a) omega-3 polyunsaturated fatty acids; b) arginine or ornithine or pharmaceutically acceptable salt of arginine or ornithine; or c) RNA, nucleotide or nucleoside; or mixtures of one or more of a), b) and c) to prevent or minimize the effects of hypoxia-reperfusion injury. When used to minimize the effects of ischemia-reperfusion injury, column 7, lines 9-13 disclose that a dietary supplement containing the foregoing can be administered over a period of three days or longer before surgery, generally three to six days before surgery. Such supplements are disclosed at column 6, lines 21-61 as comprised of energy sources in an amount supplying from 600 to 1,000 Kcal/day. Schneider et al. does not disclose or suggest administration of green tea extract for any purpose, much less to prevent or reduce postoperative complications.

Sherratt et al. discloses compositions comprising glutamine in combination with other nutrients, including N-acetyl-cysteine and Vitamins A, C, E that can be administered for promoting recovery in patients undergoing elective surgery and for treating multiple organ system failure. The compositions are administered to patients before and after elective surgical procedures, in particular 1-2 days prior to and/or after elective surgical procedures

Schneider ('829 patent) discloses the use of L-arginine, a precursor of L-arginine and/or physiologically acceptable salts thereof, or of (i) a nitric oxide donor, and/or (ii) a substrate of the nitric oxide synthetase, and/or (iii) a precursor of the said substrate, in the preparation of a medicament or nutritional formulation for the amelioration of micro-circulatory hypo-perfusion, and/or the treatment or prophylaxis of hypoperfusion-reperfusion injury, in patients which have undergone elective surgery, characterized in that the medicament or nutritional formulation is pre-operatively administered to the patient. Schneider et al. ('829 patent) discloses glutamine as a precursor of L-arginine. Schneider et al. ('829 patent) further discloses that the medicament is administered at least one day prior to surgery, but can be initiated between 3-10 days prior to surgery.

The present claims are directed to compositions and methods for averting or reducing the risk of postoperative complications. In the method of the invention a composition a

composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, and/or one precursor of this NO donor, wherein said NO donor and precursor are selected from the group consisting of glutamine, precursors of glutamine, trinitroglycerin, isosorbite dinitrate, nitroprussite, aminoguanidine, spermine-NO, spermidine-NO and SIN 1 (3-morpholinosydnone imines), or the physiologically tolerated salts or combinations thereof is gastrointestinally administered to a surgical patient less than twenty-four hours before a surgical procedure.

The claimed compositions and methods are not obvious on view of Inanami et al. (Free Radic Res), Schneider et al (U.S. Patent 6,656,608), Sherrat et al (U.S. Patent 6,423,359) and Schneider et al. (U.S. Patent 5,902,829). None of the cited references, alone or in any combination, disclose or suggest the methods of claims 3-10, 16, 18-19 and 21-25 of averting or reducing the risk of postoperative complications wherein a composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, and/or one precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, precursors of glutamine, trinitroglycerin, isosorbite dinitrate, nitroprussite, aminoguanidine, spermine-NO, spermidine-NO and SIN 1 (3-morpholinosydnone imines), or the physiologically tolerated salts or combinations thereof is gastrointestinally administered to a surgical patient less than twenty-four hours before a surgical procedure.

Applicants have surprisingly found that administration of the claimed composition to a surgical patient less than 24 hours before a surgical procedure averts or reduces the risk of postoperative complications. There is nothing in any of the cited references, alone or in any combination that suggests the claimed methods of averting or reducing the risk of postoperative complications by gastrointestinally administering to a surgical patient a composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, and/or one precursor of this NO donor before a surgical procedure wherein administration of the composition takes place less than twenty-four hours before a surgical procedure.

The Declaration of the inventor Dr. Heinz Schneider, submitted herewith, presents experimental data showing that green tea extract together with glutamine ameliorates ischemia-perfusion injury, whereas a solution of glutamine in combination with other antioxidants did

not provide protection against postoperative complications. The Declaration of Dr. Schneider additionally explains that administration of the claimed compositions less than twenty-four hours before a surgical procedure is not merely an adjustment of particular work conditions. This is because the efficacy of certain enterally applied compounds depends on gastric emptying kinetics and actual uptake from the small intestine. For this reason, it is important to administer compounds such as green tea extract and glutamine shortly before surgery, whereas other compounds such as arginine need to be given over days in order to be effective since their efficacy depends on increased blood levels. In view of the data in the declaration of D. Schneider, it would not be expected that the compositions disclosed in Sherratt et al., which contain glutamine in combination with other nutrients, including N-acetyl-cysteine and Vitamins A, C, and E, would protect against postoperative complications.

In summary, the claimed compositions and methods are not obvious in view of the combined teachings of Inanami et al. (Free Radic Res), Schneider et al (U.S. Patent 6,656,608), Sherrat et al (U.S. Patent 6,423,359) and Schneider et al. (U.S. Patent 5,902,829). Withdrawal if this section 103 rejection is respectfully requested.

At page 9 of the Office Action, the Examiner rejected claims 16 and 20 under 35 USC 103 as unpatentable over Inanami et al. (Free Radic Res), Schneider et al. (U.S. patent 5,656,608) and Jerkic et al. (Nephr Dial Trans) and further in view of Wu et al. (J. Nutr.). The Examiner stated that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the green tea extract taught by Inanami et al. and the glycine and L-arginine taught by Schneider et al. and Jerkic et al. to obtain a composition which would be useful for treating preoperative patients to reduce the risk of postoperative complications. This rejection was apparently repeated from the previous Office Action in view of claim 20 which was directed to the formulation of Claim 16, wherein component b) is arginine or an arginine precursor in the form of a di- or tripeptide.

Applicants traverse this rejection. Claim 20 has been cancelled without prejudice and this rejection is now moot with respect to this claim.

Inanami et al. discloses oral administration of (-)catechin from green tea to gerbils for two weeks prior to surgery wherein the surgery induced transient focal brain ischemia. Administration of (-) catechin continued one week after surgery. The authors found that oral

administration of (-) catechin protected the animals against ischemia-reperfusion-induced neuronal death.

Schneider et al. (U.S. Patent 5,656,608) disclose the use of one or more of the amino acids glycine, alanine and serine in combination with a) omega-3 polyunsaturated fatty acids; b) arginine or ornithine or pharmaceutically acceptable salt of arginine or ornithine; or c) RNA, nucleotide or nucleoside; or mixtures of one or more of a), b) and c) to prevent or minimize the effects of hypoxia-reperfusion injury. When used to minimize the effects of ischemia-reperfusion injury, column 7, lines 9-13 disclose that a dietary supplement containing the foregoing can be administered over a period of three days or longer before surgery, generally three to six days before surgery. Such supplements are disclosed at column 6, lines 21-61 as comprised of energy sources in an amount supplying from 600 to 1,000 Kcal/day. Schneider et al. does not disclose or suggest administration of green tea extract for any purpose, much less to prevent or reduce postoperative complications.

Jerkic et al. discloses administration of arginine, a NO substrate, to rats for four weeks prior to induction of acute renal failure. The authors found that arginine reduces tubular cell injury in acute post-ischemic renal failure. Jerkic et al. does not disclose or suggest administration of green tea extract for any purpose, much less to prevent or reduce postoperative complications.

Wu et al. provides a review of studies concerning the role of arginine on cardiovascular function and therapy. At page 2628, right column, Wu et al. discloses that studies using animal models suggest that arginine administration improves tissue preservation during reperfusion and increases regional blood flow in focal cerebral ischemia.

None of the cited references, alone or in any combination, disclose or suggest the formulation of claim 16 which comprises a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, and/or one precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, precursors of glutamine, trinitroglycerin, isosorbite dinitrate, nitroprussite, aminoguanidine, spermine-NO, spermidine-NO and SIN 1 (3-morpholinosydnone imines), or the physiologically tolerated salts or combinations thereof. The Examiner recognizes this in her comments to this rejection at page 11. Withdrawal of this section 103 rejection is respectfully requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 09600-00031-US. A duplicate copy of this paper is enclosed.

Date: September 19, 2007

Respectfully submitted,

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# APPENDIX A

# Proposed classification of complications of surgery with examples of utility in cholecystectomy

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*Lack of uniform reporting of negative outcomes makes interpretation of surgical literature difficult. We attempt to define and classify negative outcomes by differentiating complications, sequelae, and failures. Complications and sequelae result from procedures, adding new problems to the underlying disease. However, complications are unexpected events not intrinsic to the procedure, whereas sequelae are inherent to the procedure. Failures are events in which the purpose of the procedure is not fulfilled. We propose a classification of complications based on four grades: Grade I complications are alterations from the ideal postoperative course, non-life-threatening, and with no lasting disability. Complications of this grade necessitate only bedside procedures and do not significantly extend hospital stay. Grade II complications are potentially life-threatening but without residual disability. Within grade II complications a subdivision is made according to the requirement for invasive procedures. Grade III complications are those with residual disability, including organ resection or persistence of life-threatening conditions. Finally, grade IV complications are deaths as a result of complications. To illustrate the relevance of the classification, we reviewed 650 cases of elective cholecystectomy. Risk factors for development of complications were determined, and the classification was also used to analyze the value of a modified APACHE II as a preoperative prognostic score. Both supported the relevance of the proposed classification. The advantages of such a classification are (1) increased uniformity in reporting results, (2) the ability to compare results of two distinct time periods in a single center, (3) the ability to compare results of surgery between different centers, (4) the ability to compare results of surgical versus nonsurgical measures, (5) the ability to perform adequate metaanalysis, (6) the ability to identify objective preoperative risk factors, and (7) the ability to establish preoperative prognostic scores. (SURGERY 1992;111:518-26.)*

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COMPLICATIONS ARE REPORTED in every publication dealing with results of surgery because their number and severity are important measures of a surgical procedure. Complications are used as a basis to evaluate the improvement in standard surgical procedures, for selection of management options, and to compare results in individual centers and among centers. The term *surgical complication* is in general usage in the language. The possibility of complications is frequently a source of patient apprehension, and this subject constitutes an essential portion of the preoperative discussion leading to informed consent.

Recently, stimulated by the challenge to assess the future of surgical versus nonsurgical treatment of gallstones, surgical outcomes were examined. We expected to show improved mortality and morbidity rates for elective cholecystectomy during the past 30 years and argued that standard cholecystectomy was still evolving

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and improving. Two index systems from 1960 to March 1990 (Medline and Current Contents) were used to review published series of cholecystectomies. Although it is possible to show improvement in mortality rates, valid comparisons of complications are impossible because no standard reporting system exists for complications.[1-12] The large variability in results is in part the result of disagreement about which events constitute complications. For instance, one of the highest complication rates is reported by Haff et al.,[3] who include "any postoperative situation in which the patient's temperature reached 38.2° C on 2 consecutive days," whereas most authors do not consider fever to be a complication. The absence of a particular complication is rarely noted, and therefore the reader cannot know if it has been overlooked or did not occur. Disagreement occurs among authors about whether failure to cure the primary problem is a complication. For instance, some authors include retained stones, whereas others do not, some authors consider only early postoperative events to be complications, whereas others include intraoperative events or late postoperative events such as postcholecystectomy syndrome. In one report incidental carcinoma of the gallbladder is listed.[4] Although it is made apparent that this is not truly a complication, it is not clear to the authors where such information should be reported. An obvious need exists for exact definition of complications.

Estimation of severity of complications suffers from a similar lack of precision. Some authors separate minor from major[8] or "life-threatening"[2] complications without justification of the terms and often without listing lesser problems. Often complications are listed by general diagnosis such as arrhythmias, urinary tract infections, or pancreatitis but without grading of severity.[3, 5, 6, 9] In fact we did not find a comprehensive definition of severity in any article, although occasionally definition of severity can be found within a specific complication such as minor versus major pulmonary complications.[3]

It is our opinion that the lack of standardized reporting of complications and other negative outcomes in the surgical literature greatly hinders interpretation of results. What does a complication rate of 11% compared with a rate of 34% mean when the criteria are so variable? Although metaanalysis is increasingly proposed as an invaluable statistical tool able to give conclusive answers when ideal trials are missing,[13, 14] this approach is inapplicable to cholecystectomy today and, probably, to results of many other surgical procedures. The aim of this article is to define relevant terms and propose a system of classification of complications based on severity that can act as a standard reporting guide.

## DEFINING "COMPLICATIONS" AND OTHER NEGATIVE OUTCOMES OF SURGICAL PROCEDURES

A negative outcome of a procedure is simply an undesirable result. We submit that there are three types of negative results, namely complications, sequelae, and failures of therapy.

**Complications of surgical procedures.** The exact definition of a surgical complication is difficult. Although medical dictionaries define complication of a disease as "a secondary disease or condition developing in the course of a primary disease (e.g., pneumonia is a complication of measles)," they do not define surgical complication. The word complication comes from the Latin *complicare*, to fold in, suggesting combination, as in combination of problems leading to complexity and puzzlement. Dictionaries list at least five major definitions, and the elements of a surgical complication may be (1) they usually occur as a result of the procedure, (2) they are deviations from the ideal course and tend to impair or delay complete recovery, (3) they induce changes in the management of the patient (diagnostic or therapeutic), (4) they are morbid (i.e., cause suffering because of either their own effects or they expose patients to additional diagnostic and therapeutic procedures), and (5) they occur during the performance or recovery from the procedure (i.e., within the time that uncomplicated procedures reach recovery), although exceptions do exist.

**Sequelae of surgical procedures.** The common definition of sequela is an "aftereffect." A sequela is another negative outcome resulting, like complications, from the surgical procedure, but it may appear after recovery from the procedure and tends to be persistent. However, the distinguishing feature of a sequela is that the problem is inherent to the procedure (i.e., it is an accepted alteration in structure or function of the body that is embodied in the procedure). Surgical scars are sequelae just as keloids are, even though they occur only occasionally. The reduction in pulmonary function after pneumonectomy or reduction in gastrointestinal function after massive bowel resection is also a sequela. Likewise, dumping syndrome and postvagotomy effects should be considered sequelae.[15] Although their occurrence is less predictable, they are produced by the nature of the operation, which introduces an alteration in gastrointestinal motility, storage, or secretion. However, some events may contain elements of both sequelae and complications, such as severe postoperative pain, postoperative paralytic ileus, or lung emboli after splenectomy with postoperative thrombocytosis. We suggest that such events should be considered complications.

**Failures of surgical therapy.** Failure implies that the original purpose of the procedure is not fulfilled. Surgical procedures may be well executed and uncomplicated yet fail. The most common example is recurrence of tumor. Retained or recurrent common bile duct stones are another example, because the purpose of cholecystectomy is to eradicate stone disease. The difference between a failure and either a complication or a sequela is that one fails to permanently eradicate the original problem, whereas the other adds a new element to the problem.

Although all three classes of negative outcomes should be reported to assess results of procedures completely, the remainder of this discussion will be limited to surgical complications.

## A GENERAL CLASSIFICATION OF COMPLICATIONS BY SEVERITY

A classification of complications should be applicable to most surgical situations that do not correspond with the ideal course. In selecting the basis for stratification, one might consider either degree of morbidity caused by the complication or economic effect. Although not mutually exclusive, one classification cannot easily contain both. A classification based on patient morbidity has many advantages and does not preclude computation of direct or indirect cost. To stratify severity of complications based on morbidity, the following criteria were used: (1) whether the complication is life-threatening (i.e., if left unchecked would the event normally resolve or go to permanent disability or even death?), (2) whether interventions required as a result of the complication carry significant risks (with particular negative weighting given to invasive procedures), and (3) whether residual disability or death is induced by the complication. We place great reliance on the therapeutic procedure required to treat the complication to indicate the severity of the complication. The complication may not be described in detail, but documentation of diagnostic tests and treatment is usually adequate; this is particularly true in retrospective analysis. Another reason for considering diagnostic procedures and treatments in a classification resides in the fact that they induce further morbidity. This approach also tends to eliminate subjective interpretation of severity and a tendency to down-rate complications because it is based on hard criteria.

Although relevant in evaluating the cost of a procedure, duration of hospital stay was not generally used because it is influenced by the availability of facilities and by different policies in individual centers. However, to consider a complication to be at the lowest level is inappropriate if it induces a prolonged hospital stay, even if it meets the other criteria. Iatrogenic injuries likewise receive special consideration in this classification. The general classification is intended as a guide for establishing specific classifications for individual surgical procedures and contains principles rather than details. Subsequently we will derive a specific classification for cholecystectomy as an example of how the general rules may be applied.

It is our opinion that almost all documented deviations from the ideal postoperative course (i.e., sometimes even if asymptomatic such as cardiac arrhythmia) should be recorded as complications. Although the identification of asymptomatic events depends on the strength of controls, their incidence may be important when the procedure has to be transposed to a high-risk or aged population.

**Grade I.** Grade I complications include all events carrying minor risks. The term *minor* means that the complication, if left untreated, has a spontaneous resolution, can be cleared by the patient after instruction, or at most requires a simple bedside procedure with no or minor analgesia. Drugs are not required other than analgesic, antipyretic, antiemetic, and antidiarrheal drugs or drugs required for urinary retention or low urinary tract infection. No iatrogenic injuries are included here. Only complications that do not result in a hospital stay greater than twice the median hospitalization for the procedure are included in this group. This is intended to maintain grade I as a truly low-morbidity category.

**Grade II.** Grade II complications differ from grade I in that they are potentially life-threatening and usually require some form of intervention, which is associated with well-described complications. Grade II events differ from grade III complications mainly in that they neither produce lasting or residual disability nor result in organ resection. As mentioned above, complications resulting in a doubling of the mean hospital stay are put into the grade II category. Iatrogenic injuries except those resulting in residual disability, organ resection, or death are included here.

A large spectrum of complications is included in this category related to the suffering that the complications may cause to patients, as well as the risk inherent in some invasive procedures needed to treat the complication. Therefore a subdivision into two strata of severity is proposed according to the invasiveness of the interventions needed to manage the complication. Grade IIa includes all complications requiring drug therapy other than that allowed for grade I, total parenteral nutrition, or transfusion for postoperative bleeding. Grade IIb complications are those requiring invasive procedures

including therapeutic imaging procedures (e.g., percutaneous drainage of abscess), therapeutic endoscopy, or reoperation. Iatrogenic injuries requiring operative procedures, even when performed during the same operation, should be included here.

**Grade III.** Grade III complications are events with residual or lasting disability (e.g., lasting organ deficiency including organ resection). A myocardial infarct is in this category as is any cerebrovascular event with residual disability. Complications such as common bile duct stenosis compromising liver function and gastrointestinal stenosis that impairs digestive function are grade III. Infections such as gas gangrene or necrotizing fasciitis that result in tissue loss and impairment of function would also be placed in this category. Organ resection caused by surgical error is equated with residual disability. Of course, when the organ resection is planned (e.g., splenectomy or amputation), the lasting disability is a sequela and not a complication.

**Grade IV.** Grade IV events are deaths as a result of any complication.

The classification may be illustrated by two examples: postoperative pancreatitis and postoperative wound infection. Appraisal of the severity of acute pancreatitis occurring after abdominal surgery is difficult. According to our scale, asymptomatic hyperamylasemia or mild pancreatitis treated conservatively without a significant increase of the hospital stay is a grade I complication; acute pancreatitis resulting in a long hospital stay would be a grade IIa complication. When treated by invasive modalities including endoscopic sphincterotomy, percutaneous drainage of fluid collections, or laparotomy for drainage, the category would be IIb. When organ resection is required or if diabetes or steatorrhea occur, the pancreatitis would be considered as grade III. Grade IV requires no comment. A postoperative wound infection is grade I if it can be treated by simple reopening of the wound and packing. Prolongation of hospital stay to greater than twice the median stay for the procedure would make it grade IIa. A deeper or more serious infection requiring debridement under general anesthesia or reopening of the abdomen or percutaneous drainage would make it grade IIb. The requirement for substantial tissue loss resulting in functional impairment or requiring reconstructive procedures would make it a grade III complication.

## PROPOSED SPECIFIC CLASSIFICATIONS OF COMPLICATIONS OF CHOLECYSTECTOMY

As noted above, mortality rates from cholecystectomy are low, and this variable alone is not an appropriate way to compare results of standard cholecystectomy with those of other procedures; a finer scale of negative outcomes is needed. Although the proposed classification is directed primarily toward assessment of results of surgery, it is also useful in comparing surgical and nonsurgical procedures.

In the Appendix we have attempted to grade the postoperative complications associated with cholecystectomy. In our institution the median hospital stay for elective cholecystectomy alone or associated with common bile duct exploration is 6 and 12 days, respectively. Therefore a complication resulting in a hospitalization of more than 12 or 24 days, respectively, represents a significant increase in the hospital stay for this procedure and will be identified at least as a grade IIa complication. As mentioned previously, intraoperative injuries should be reported as at least grade II complications. Residual bile duct stenosis and persistent signs of liver injury are considered to be grade III.

What is the minimum follow-up period to properly identify complications of cholecystectomy? Because the length of hospitalization depends mostly on clinician and hospital policy, recording complications occurring only during the hospital stay is inappropriate. Almost all complications related to cholecystectomy occur during the first 4 postoperative weeks; thus to propose a minimum follow-up of 6 weeks seems reasonable. Obviously, additional information in terms of negative outcomes is obtained by longer periods of observation. For comparative purposes it would be ideal if agreement could be reached regarding standard length of follow-up as we now do for malignancies. For cholecystectomy, follow-up periods of 6 weeks, 1 year, or 5 years, depending on the purpose of the study (i.e., whether to examine complications, sequelae, or failures), may be reasonable.

**Use of the classification to examine surgical outcome of cholecystectomy relative to risk.** To illustrate the utility of the classification, we reviewed the records of 650 consecutive patients who underwent elective cholecystectomy at Mount Sinai Hospital, Toronto, between January 1984 and December 1989. All patients were referred to the senior author (S.M.S.). The mean age was 48 years (range, 16 to 88 years). One hundred seventy-two of the patients were men (mean age, 53 years), and 478 patients were women (mean age, 46 years). In 56 cases the common bile duct was explored, and six patients required biliary-digestive anastomoses. A 6-week follow-up was available in all patients. In this series no deaths occurred, but 78 patients (12.0%) had complications. Grade I complications only were recorded in 38 patients (5.9%), the most common being postoperative fever greater than 38.5° C

**Table I.** Univariate analysis of risk factors related to complications after elective cholecystectomy

| | *Number of patients (% of the total 650 patients)* | *Overall complications* | | *Grade I complications* | | *Grade II complications* | |
|---|---|---|---|---|---|---|---|
| | | *OR* | *95% CI of the OR* | *OR* | *95% CI of the OR* | *OR* | *95% CI of the OR* |
| Age (yrs) | | | | | | | |
| <45 | 299 (46.0) | 0.33 | 0.19-0.57 | 0.48 | 0.24-1.02 | 0.22 | 0.10-0.51 |
| 45-65* | 239 (36.8) | 1.88 | 1.02-3.47 | 1.87 | 0.88-3.98 | 1.89 | 0.71-5.03 |
| >65 | 112 (17.2) | 4.33 | 2.60-7.21 | 1.93 | 0.88-4.25 | 8.42 | 4.31-16.47 |
| Male | 172 (26.5) | 2.78 | 1.40-3.71 | 2.26 | 1.16-4.42 | 2.30 | 1.19-4.42 |
| Obesity | 120 (18.5) | 1.37 | 0.78-2.44 | 1.22 | .55-2.78 | 1.54 | 0.72-3.22 |
| Diabetes | 27 (4.2) | 1.69 | 1.59-4.55 | 1.39 | .31-6.25 | 2.00 | 0.58-7.14 |
| Cardiovascular disorders | 54 (8.3) | 5.00 | 2.63-39.09 | 2.33 | .85-6.25 | 8.33 | 4.00-16.67 |
| Immunodeficiency | 26 (4.0) | 8.33 | 3.85-19.23 | 5.00 | 1.57-16.39 | 12.50 | 5.00-33.33 |
| Liver cirrhosis | 7 (1.1) | 1.22 | 0.15-10.00 | >20 | <0.10->100 | 2.44 | 0.28-20.00 |

Odd ratios (OR) for patients developing overall complications, grade I and II complications are compared to the group of patients without complications.
*CI*, Confidence interval.
*Group of age 45 to 65 years is compared to younger patients.

(37%) and urinary tract disorders (26%). Forty patients (6.2%) had grade II complications, including four patients with grade IIb complications (two cases of bile leak requiring intervention, one case of intraabdominal abscess drained percutaneously, and one case of incarcerated femoral hernia requiring urgent operation). There were no grade III complications. Because of the small number of grade IIb complications, grades IIa and IIb are considered together for the purpose of this analysis.

*Risk factors.* The risk of postoperative complications arising from preoperative conditions is still not well established for cholecystectomy. Age, sex, obesity, diabetes, cardiovascular diseases, immunologic disorders, and liver cirrhosis have been incriminated occasionally as risk factors.[5-9, 16-22] These conditions were reviewed in our series of 650 patients. Diabetes refers to patients who were taking oral hypoglycemic drugs or insulin or patients with a fasting serum glucose level greater than 200 mg/dl (11 mmol/L). Obese patients were identified according to the Quetelet index (weight in killiograms)/(height in meters) squared, and values greater than 28 $kg/m^2$ were considered abnormal, regardless of age and sex.[23] Cardiovascular disorders were defined as class III or IV of the New York Heart Association.[24] Patients were considered to be immunodeficient if they had cancer or human immunodeficiency positive virus results or if they were treated by radiotherapy, corticotherapy, or other chemotherapeutic agents within 3 months before surgery.

Risk factors are presented in Table I in terms of odds ratios. This approach was chosen because it gives direct quantitative information on the risk of developing a complication when exposed to the factor in question. An odds ratio equal to 1 indicates that the risk of developing complications is similar with or without the factor studied. A ratio of more than 1 indicates a positive association between the factor and a complication. A value of less than 1 gives the opposite interpretation. Statistical significance is achieved when 95% confidence intervals of odd ratios, determined according to the method described by Dersimonian and Laird,[25] does not include the value 1.0.

Table I shows that there was a significant risk of developing a complication when the patient was older, male, diabetic, had cardiovascular disorders, or was immunodeficient. Note, however, that except for maleness and immunodeficiency none of these preoperative factors was predictive of a grade I complication. The factors predictive of grade II complications were age, maleness, cardiovascular disorders, and immunodeficiency.

What can be learned from this data according to the classification of complications? If overall complications are viewed alone, one could conclude that age, maleness, diabetes, cardiovascular disorders, and immunodeficiency are predictive of complications, although one would have no information whether these factors were predictive of lesser or more serious complications. The analysis shows that only maleness and immunodeficiency are predictive of grade I complications, whereas advanced age, maleness, cardiovascular disorders, and immunodeficiency are predictive of more serious complications; this is additional information. The analysis also shows that we know little about the risk factors for grade I complications, because few of the factors exam-

**Table II.** Preoperative modified APACHE II score related to complications after elective cholecystectomy

| Modified APACHE II score (pts) | Number of patients (% of the total 650 patients) | Overall complications | | Grade I complications | | Grade II complications | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI of the OR | OR | 95% CI of the OR | OR | 95% CI of the OR |
| 0-5 | 556 (85.5) | 0.13 | 0.08-0.23 | 0.25 | 0.12-0.53 | 0.08 | 0.04-0.16 |
| 6-9* | 53 (8.2) | 5.04 | 2.64-9.02 | 3.83 | 1.83-8.99 | 7.01 | 2.92-16.83 |
| ≥10 | 41 (6.3) | 9.36 | 4.69-18.66 | 1.42 | 0.77-7.59 | 17.43 | 7.95-38.21 |

*OR*, Odds ratio; *CI*, confidence interval.
*"APACHE II score "6 to 9 points" is compared to score "0 to 5 points."

ined were found to be important. This should lead to the proposal of other potential risk factors and perhaps identification of significant ones. Note also that diabetes drops out as a significant predictive factor when the analysis is done in terms of grades I and II complications. This is to be expected when a factor relates to both grades of complications, but not enough data exists to achieve significance in individual analyses. This points out a difficulty that would be encountered if variables were related to specific complications (e.g., age to wound infection) or if extensive subclassification is done. A good classification should provide new insights and minimize the chance of such type 2 errors. We would emphasize that this analysis requires extension to a multivariate form to identify independent significant risk factors. This is being done, but it is not our purpose to present in detail an analysis of risk factors for cholecystectomy but rather to show certain uses of the classification of complications. Many related questions might be approached once such a classification is standardized.

**Preoperative severity score.** To explore another possible utility of the classification system, we examined the value of a preoperative scoring system, namely a modified APACHE II score, to predict complications. APACHE II is designed to predict the outcome of patients in intensive care units[26] and has been shown to be useful to assess the severity of other diseases.[27-31] Our preoperative APACHE II score was based on only two sets of criteria: (1) age: less than 45 years (0 points), 45 to 54 years (2 points), 55 to 64 years (3 points), 65 to 74 years (5 points), and greater than 74 years (6 points); and (2) concomitant disorders: 5 points for the presence of a history of severe organ system insufficiency, as proposed initially by Knaus et al.[26] Such a scoring system might be very useful because it is simple and easy to apply.

Three patient groups were examined for prediction of risk: low risk, 0 to 5 points; intermediate risk, 6 to 9 points; and high risk, more than 9 points. These categories were chosen without knowledge of the particular complications, and the results are shown in Table II. Note that the modified APACHE II score would predict a difference in total number of complications between the low-risk group and the other two groups in which the odds ratio was significantly greater than 1.0. A significant risk exists for grade I complications in the intermediate group, but interestingly no such risk exists in the high-risk group. It may be that particular attention was given to the high-risk patients including prophylactic measures such as intensive respiratory physiotherapy and intensive postoperative observation, thus preventing minor complications. On the other hand, both intermediate and high-risk groups have a significant chance of developing a grade II complication, but the odds ratio for these complications is much higher in the high-risk group (17.4) than in the intermediate group (7.0). Again, to determine whether the modified APACHE II score is predictive, a prospective analysis will be required. It may be possible to derive improved prognostic indices by alteration of criteria based on identification of the importance of individual risk factors particular to cholecystectomy. Although this will require considerable additional work, these examples show how the classification can be used to develop predictive scores for surgical procedures.

Although the preceding examples may be of some interest, we strongly believe that the most important benefits of a standard classification will be the ability to compare data among centers and across time and to permit metaanalysis or the grouping of like studies to obtain information that cannot be seen in individual studies. This technique has provided valuable information in other areas, and it seems highly probable that it would add considerably to our understanding of expected complications. Initially we had believed that a classification might allow us to categorize complications retrospectively in the reported literature, but as discussed the reporting of type and severity of complications is so variable that this could not be done.

## DISCUSSION

We have shown shortcomings in the current methods of presenting the negative outcomes of surgery, particularly complications, and have proposed a general classification of complications and applied this classification specifically to cholecystectomy. We have also shown the potential value of the classification in examining important surgical issues. This classification is a proposal, the aim of which is to stimulate discussion that will lead to a consensus and a common method of reporting complications. The eventual aim should be to obtain a complete and standardized way of reporting all negative outcomes for operative and nonoperative procedures.

As with any classification of this type, some separations must be based on somewhat arbitrary criteria. Inevitably some events overlap two levels of the severity scale or combine elements of a complication, sequela, or failure. For this reason a general classification can be used only as a guide to the development of specific classifications that exactly detail particular complications related to the procedure in question; otherwise misclassification will be common.

A balance must be attained between the extent of subclassification and the utility of the classification. Less subclassification leads to groups with a broad range of members and a dissatisfaction in the sense that members at the extreme ends of a subgroup do not seem to belong in the same category. More subclassification reduces this problem but makes application of the classification more time-consuming and difficult to use and also less likely that it will be used. More important, multiple subgroups increase the risk of type 2 errors. For these reasons grade II complications were lumped together in the analyses presented. It may even be necessary to combine grades II and III for purposes of analysis in some instances in which the incidence of complications is particularly low. On the other hand, this is where metaanalysis would be important, because with very large numbers of patients presented in a standard way the subclassification could be retained and valid correlations to risk factors made. For other procedures that carry more risk and where the incidence of complications is higher, such as transplantation, further subclassification within grade II or III might be possible and worthwhile.

A particular problem in the classification of complications is iatrogenic injury. Most minor iatrogenic injuries such as a serosal bowel laceration or a splenic capsular tear are never reported unless they lead to postoperative problems; nor is it likely to be valuable to insist on collection of such information. Often the most minor iatrogenic injuries are part of a surgical procedure, particularly when that procedure is difficult. As an example, a serosal tear may occur in the presence of severe inflammation or dense adhesions, and one does not usually consider this to be a complication. For these reasons we have not included a lesser level of iatrogenic injury. However, many iatrogenic injuries are truly complications and should be included in the classification system.

This classification applies to only one type of negative outcome, namely complications. Negative outcomes also include sequelae and failures. This is particularly important if comparisons of procedures are to be made. For instance, in the treatment of cholelithiasis, complications are likely to be more common with surgery, but failures to cure including recurrences are likely to be more common with nonsurgical therapies. The latter are occasionally downplayed by suggestions that failure of a nonsurgical therapy is not a negative outcome because surgery can always be done. It is unlikely that those who must be satisfied with the treatment (i.e., our patients or those paying for procedures) would agree with this view. Perhaps for certain procedures, complications, failures, and sequelae are best classified together, but we doubt that this will be efficient. It is more probable that a severity system should be developed to examine failures and sequelae of surgery. Classification of failures and sequelae must also be very specific if they are to be useful.

In summary, we have presented a systematic approach to the classification of complications and its possible uses, advantages, and disadvantages. Considerable additional work is required before such a standard classification can be adopted; yet we believe the effort is worthwhile because the adoption of a standardized severity system will allow us (1) to increase uniformity in reporting results, (2) to compare results of two distinct periods in a single center, (3) to compare results of surgery between different centers, (4) to compare results of surgical versus nonsurgical measures, (5) to perform adequate metaanalysis, (6) to identify objective preoperative risk factors, and (7) to develop a prognostic scoring system.

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## APPENDIX: CLASSIFICATION OF COMPLICATIONS OF CHOLECYSTECTOMY

| | |
|---|---|
| **Grade I:** | No events must be included here unless fulfilling the general characteristics: (1) not life-threatening; (2) not requiring use of drugs other than analgesic, antipyretic, antiemetic, antidiarrheal, and drugs required for urinary retention or low urinary tract infection; (3) requiring only interventions that can be performed at the bedside; (4) never associated with hospital stay greater than twice the median stay for the procedure |
| Cardiac: | Asymptomatic arrhythmias and electrocardiographic modifications not requiring treatment |
| Respiratory: | Atelectasis cleared by physiotherapy alone |
| Gastrointestinal: | Gastric distension treated by nasogastric suction and pancreatitis not requiring specific therapy |
| Urinary: | Retention treated medically or by catheterization alone and low urinary tract infections treated with antiseptics |
| Local: | Superficial wound infection and wound hematoma |
| Other: | Fever greater than 38.5° C on two occasions and resolving spontaneously in less than 48 hours |
| **Grade II:** | Any complication that is potentially life-threatening or results in hospital stay greater than twice the median stay for the procedure but does not result in residual disability or organ resection |

| | |
|---|---|
| **Grade IIa:** | Complications requiring only use of drug therapy, total parenteral nutrition, or blood transfusion |
| Cardiac: | Arrhythmias or electrocardiographic modifications requiring treatment, angina pectoris, and hypertensive crisis |
| Respiratory: | Pneumonia or other pulmonary conditions for which antibiotics are used, lung emboli, and transient respiratory failure |
| Gastrointestinal: | Acute pancreatitis treated medically including total parenteral nutrition |
| Urinary: | Symptomatic urinary tract infection or retention with signs of bacteremia treated medically and renal failure not requiring dialysis |
| Local: | Wound infections requiring antibiotics and evidence of continuing bleeding after surgery managed by transfusion alone |
| Other: | Bacteremia, fever greater than 38.5° C for more than 48 hours, and any complication resulting in hospital stay greater than twice the median stay for the procedure |
| **Grade IIb:** | Complications requiring therapeutic imaging procedures,therapeutic endoscopy, or reoperation; all other life-threatening complications not fitting grade IIa or III criteria |
| Respiratory: | Bronchial obstruction requiring bronchoscopy or reintubation for pulmonary failure |
| Gastrointestinal: | Gastrointestinal hemorrhage requiring therapeutic endoscopy, postoperative bowel obstruction requiring reoperation, and pancreatitis requiring therapeutic endoscopy, drainage, or surgery |
| Urinary: | Urinary retention requiring therapeutic endoscopic or surgical procedures and renal failure requiring transient dialysis |
| Local: | Wound infections requiring debridement under general anesthesia, intraabdominal abscesses, bile or blood collections requiring drainage by imaging procedures or reoperation, iatrogenic injury including bile duct injury treated by T-tube or biliary anastomosis but without residual narrowing, and full-thickness intestinal injuries |
| Other: | Stroke that resolves |
| **Grade III:** | Any complications with residual and lasting disability and the presence of persistent and objective signs of life-threatening diseases or organ resection |
| Cardiac: | Myocardial infarction, impending infarction, and unstable angina |
| Respiratory: | Any disorder with long-lasting respiratory failure |
| Gastrointestinal: | Acute pancreatitis with residual diabetes or steatorrhea |
| Urinary: | Any disorders with residual renal insufficiency |
| Local: | Complete transection of a lobar bile duct, common bile duct, or common hepatic duct with residual narrowing and hepatic artery or left or right main branches with persistent radiologic, histologic, or enzymatic abnormalities in liver function |
| Other: | Stroke with residuals |
| **Grade IV:** | Death in a patient as a result of a complication |